CARDIOVASCULAR MEDICINE

# Changes in the Doppler myocardial performance index during dobutamine echocardiography: association with neurohormonal activation and prognosis after acute myocardial infarction

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**Objectives:** To test whether an increase in Doppler myocardial performance index (MPI) during dobutamine stress echocardiography, reflecting deterioration of overall left ventricular function, is associated with increased N-terminal pro-brain natriuretic peptide (NT-pro-BNP) concentration and provides prognostic information beyond conventional systolic wall motion analysis after acute myocardial infarction (AMI).

**Design:** Prospective, observational study.

**Methods:** Dobutamine–atropine stress echocardiography (DASE) and NT-pro-BNP were assessed five days after AMI in 109 consecutive patients. MPI was measured at rest and at low-dose (10 μg/kg/min) and peak dobutamine infusion (⩽ 40 μg/kg/min with or without atropine).

**Main outcome measures:** End point was a composite of cardiac death or readmission for heart failure or reinfarction.

**Results:** In 35 patients (32%), MPI increased at low-dose DASE. This was associated with higher NT-pro-BNP concentrations (β = 0.30, p = 0.004). During a mean follow up of 27 (SD 7) months, 8 patients died of cardiac causes and 15 patients were readmitted for heart failure or reinfarction. On Cox regression analysis, an increase in MPI at low-dose DASE (p = 0.02) was an independent predictor of cardiac events. In contrast, traditional wall motion analysis during DASE provided no additional prognostic information.

**Conclusions:** An increase in MPI at low-dose DASE, reflecting early deterioration of overall left ventricular function, is associated with raised NT-pro-BNP concentration and provides prognostic information beyond conventional stress echocardiographic data after AMI.

Inducible myocardial ischaemia may be detected and quantified by dobutamine–atropine stress echocardiography (DASE) after acute myocardial infarction (AMI). The detection of ischaemia is based on semiquantitative wall motion analysis, however, which assesses only left ventricular (LV) systolic function. The Doppler echocardiographic myocardial performance index (MPI) is a quantitative measure of combined LV systolic and diastolic function.[1–3] Because impaired LV diastolic function precedes LV systolic dysfunction during myocardial ischaemia,[4] quantitative assessment of changes in both systolic and diastolic LV function seems appealing and may potentially increase the clinical yield of DASE after AMI. Data on the changes in MPI during stress echocardiography are limited. Recently, MPI was found to correlate closely with invasive measures of LV systolic function during β adrenergic stimulation.[5] Furthermore, we have previously shown that MPI consistently improves, decreasing its value, during dobutamine stimulation in healthy people,[6] and MPI has been shown to increase (deteriorate) during dobutamine-induced ischaemia in patients with known or suspected coronary artery disease.[7]

Brain natriuretic peptide (BNP) is a cardiac neurohormone that is secreted from the atria and ventricles in response to myocardial stretch, pressure overload and myocardial ischaemia.[8] BNP is increased in patients with systolic as well as patients with diastolic dysfunction, where it correlates with functional class and prognosis.[9–12] Furthermore, it has been suggested that raised BNP concentration is associated with inducible ischaemia among patients with coronary artery disease.[13 14] Therefore, we hypothesised that an increase in MPI during DASE after a first AMI, as an indicator of deterioration in overall LV function, is associated with increased N-terminal pro-BNP (NT-pro-BNP) concentration and increased risk of cardiac events during follow up.

## METHODS

From March 2000 to October 2001, we prospectively studied 135 consecutive patients admitted to Svendborg Hospital, Denmark with a first AMI. The diagnosis of AMI was based on a documented transient rise of biochemical markers of myocardial necrosis (creatine kinase B and troponin T), the presence of typical symptoms, or ECG signs of AMI. DASE and NT-pro-BNP concentration were assessed five days after hospital admission in 109 patients. DASE was not performed in 26 patients due to death before day 5 (n = 8), subacute revascularisation procedures (n = 9), mural thrombus (n = 2), postinfarction ventricular septal defect (n = 2), second-degree atrioventricular block (n = 1) or declining to participate in the study (n = 4), leaving a total of 109 patients (81%).

The attending physician decided on the acute management of AMI. Patients with ST segment elevation AMI presenting within 12 h of symptoms were treated with a thrombolytic.

**Abbreviations:** AMI, acute myocardial infarction; BNP, brain natriuretic peptide; DASE, dobutamine–atropine stress echocardiography; LV, left ventricular; MPI, myocardial performance index; NT-pro-BNP, N-terminal pro-brain natriuretic peptide

According to national guidelines at the time of enrolment of patients in the study, patients underwent a bicycle exercise ECG at hospital discharge. If the exercise test suggested inducible ischaemia or if symptoms suggested postinfarction angina, patients were referred for coronary angiography and underwent subsequent coronary revascularisation when appropriate. To avoid selection bias, referral for angiography was not based on DASE and the referring physicians were blinded to the results of DASE. The protocol was approved by the regional scientific ethics committee, and all enrolled patients gave informed, written consent.

### Dobutamine–atropine stress echocardiography

β blocking agents were discontinued at least 24 h before DASE. Dobutamine was administered with 3 min dose increments, starting with 5 μg/kg/min and increasing to 10, 20, 30 and 40 μg/kg/min under continuous ECG monitoring. If the patient did not reach 85% of the maximum age-predicted heart rate with dobutamine, atropine was added intravenously in 0.25 mg increments, to a maximum of 1 mg, to the continuing 40 μg/kg/min dobutamine infusion. Echocardiograms were obtained at baseline, low dose (10 μg/kg/min), and peak dose (with or without atropine) on a Sonos 5500 ultrasound machine (Hewlett Packard, Andover, Massachusetts, USA) and stored digitally for subsequent off-line analysis. The time intervals in MPI were interpreted without knowledge of regional wall motion analyses and clinical data.

### Assessment of systolic function

Wall motion score index (WMSI) was obtained semiquantitatively by dividing the LV into 16 segments.[15] Inducible ischaemia was defined as (1) a new inducible wall motion abnormality; (2) a biphasic response of the resting wall motion abnormality (improvement at low dose with worsening at peak dose); or (3) worsening of the resting wall motion abnormality at peak dose without improvement at low dose. Worsened wall motion was defined as a change from normal wall thickening to hypokinesia, akinesia or dyskinesia and from hypokinesia to akinesia or dyskinesia, but not from akinesia to dyskinesia.[16] Myocardial viability was defined as improved wall motion in $>2$ contiguous infarct-zone segments or in all infarct-zone segments, if fewer than three segments were asynergic.[17] At rest, LV volumes and ejection fraction were estimated by Simpson's biplane method.[15] LV volumes were corrected for body surface area.

### Doppler technique

MPI was defined as the sum of isovolumic contraction and relaxation times divided by ejection time, which can be obtained from pulsed Doppler recordings of mitral inflow and LV outflow.[18] Mitral inflow was recorded with the transducer in the apical four-chamber view with a 2 mm sample volume placed between the tips of mitral leaflets during diastole. The LV outflow velocity curve was recorded from the apical long-axis view with the sample volume positioned just below the aortic valve. From the inflow profile, the time from cessation to onset of inflow (A) was measured corresponding to the sum of isovolumic contraction time, ejection time and isovolumic relaxation time. From the outflow, ejection time (B) was measured. MPI was calculated as $(A - B)/B$.[18] On the basis of our previous study,[6] we chose to categorise patients according to whether an decrease (improvement) or increase (deterioration) in MPI was observed after low-dose dobutamine infusion or peak DASE, respectively. Thus, as the cut off was prespecified, the possibility cannot be excluded that some patients were categorised incorrectly due to the intraobserver and interobserver variabilities in MPI measurements. The isovolumic times and ejection time were corrected for heart rate by dividing the individual time intervals by the square root of the ECG RR interval (in seconds) between two consecutive beats.

LV filling was categorised as normal (grade 0), impaired relaxation (grade 1), pseudonormal (grade 2), or restrictive (grade 3) by combined assessment of the flow propagation velocity, obtained by colour M mode Doppler echocardiography, and E wave deceleration time as validated previously.[19] Five consecutive beats were measured and averaged for each Doppler variable for patients in sinus rhythm, whereas 10 consecutive beats were averaged for patients in atrial fibrillation.[20]

### Assessment of NT-pro-BNP

Peripheral blood samples for NT-pro-BNP determination were drawn from venepuncture after a 30 min supine rest before stress echocardiography. Test tubes were placed immediately on ice and centrifuged within 30 min at 4℃. The serum was stored at −80℃ until assayed. NT-pro-BNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics).

### Statistical analysis

Continuous data are expressed as mean (SD). Groups were compared by $\chi^2$ test for categorical variables and by two-way analysis of variance with Bonferroni corrected post hoc test for continuous variables. NT-pro-BNP data are presented as median and interquartile range. Because of skewed data distribution, NT-pro-BNP concentrations were logarithmically transformed for statistical analysis.

Cumulative survival was analysed with Kaplan–Meier plots, and differences between subgroups were tested with the log rank test. Risk was further estimated by Cox proportional hazards models. A multivariate model with forced entry was used to identify independent predictors of cardiac events. The assumptions of the proportional hazards model (proportional hazards, linearity of continuous parameters and lack of interactions) were tested and were valid unless otherwise specified. A value of $p < 0.05$ was considered significant. SPSS V.10.0 (SPSS, Chicago, Illinois, USA) was used for calculations.

### Reproducibility

MPI at rest, low dose, and peak stress was reanalysed for 25 patients by the same observer and by a second observer on separate occasions but based on the same recordings. Variability was assessed as the mean percentage error (the absolute difference divided by the average of the two observations)

## RESULTS

DASE and NT-pro-BNP concentrations were assessed 5 (SD 1) days after hospital admission. Patients were divided into

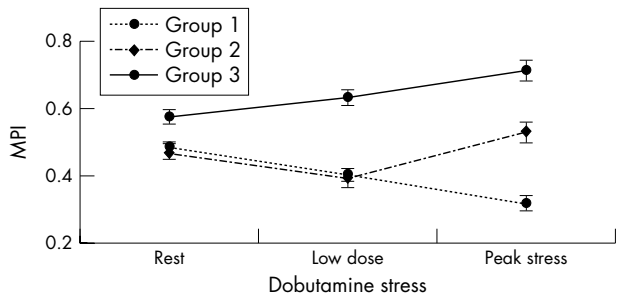


**Figure 1** Graphs showing changes in myocardial performance index (MPI) from rest to low-dose and peak dobutamine stress in the three study groups. Data are plotted as mean (SEM).

**Table 1** Clinical characteristics

| | All patients (n = 109) | Group 1 (n = 21) | Group 2 (n = 53) | Group 3 (n = 35) |
|---|---|---|---|---|
| Age (years) | 65 (11) | 63 (13) | 62 (9) | 71 (10)*† |
| Men | 75 (69%) | 14 (67%) | 38 (72%) | 23 (66%) |
| Current smoking | 51 (47%) | 6 (29%) | 26 (49%) | 19 (54%) |
| History of hypertension | 28 (26%) | 3 (14%) | 16 (30%) | 9 (26%) |
| Diabetes | 15 (14%) | 3 (14%) | 7 (13%) | 5 (14%) |
| Atrial fibrillation | 3 (3%) | 0 (0%) | 1 (2%) | 2 (6%) |
| ST elevation AMI | 69 (63%) | 13 (62%) | 31 (59%) | 25 (71%) |
| Anterior AMI | 43 (39%) | 8 (38%) | 17 (32%) | 18 (51%) |
| Killip class ⩾II during hospitalisation | 42 (33%) | 2 (10%) | 13 (25%) | 18 (51%)*† |
| Creatine kinase (IU/l) | 1552 (1497) | 1233 (1303) | 1399 (1152) | 2286 (1862)*† |
| Thrombolytics | 47 (43%) | 9 (43%) | 22 (42%) | 16 (46%) |
| Drugs at discharge | | | | |
| Aspirin | 109 (100%) | 21 (100%) | 58 (100%) | 35 (100%) |
| β blockers | 100 (92%) | 19 (91%) | 50 (99%) | 31 (89%) |
| ACEI/AIIA | 33 (30%) | 6 (29%) | 25 (47%) | 19 (54%) |
| Diuretics | 38 (35%) | 4 (19%) | 17 (32%) | 17 (39) |
| Multivessel disease‡ | 28 (32%) | 2 (13%) | 16 (33%) | 10(44%)* |
| PCI during follow up | 39 (36%) | 5 (24%) | 23 (43%) | 11 (31%) |
| CABG during follow up | 32 (29%) | 3 (14%) | 19 (36%) | 10 (29%) |
| PCI or CABG during follow up | 71 (65%) | 8 (38%) | 42 (79%)* | 21 (60%) |
| NT-pro-BNP (pmol/l) | 131 (53–260) | 56 (33–118) | 96 (47–154) | 310 (199–566)*† |

Data presented as mean (SD), number (%) of patients or median (interquartile range).
*p<0.05 versus group 1; †p<0.05 versus group 2; ‡88 (81%) patients underwent angiography.
ACEI/AIIA, angiotensin converting enzyme inhibitor or angiotensin II antagonist; AMI, acute myocardial infarction; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

three groups on the basis of the MPI response during DASE. Group 1 comprised 21 patients with an improved (decreased) MPI at low dose and a further improvement at peak dobutamine infusion; group 2 comprised 53 patients with a biphasic response (initially, MPI decreased at low dose but increased above the resting value at peak stress); and group 3 comprised 35 patients with increased (deteriorating) MPI at low dose and at peak dobutamine infusion (fig 1). Three patients, whose MPI did not change during low-dose dobutamine echocardiography but increased at peak DASE, were categorised in group 3.

The clinical and echocardiographic characteristics of the groups are listed in tables 1 and 2, respectively. Coronary angiography was performed in 88 patients (81%) at a mean of 1.6 (1.2) months after AMI. Three-vessel disease was present in 28 patients (32%) and was more common in group 3 patients than in group 1 and 2 patients (table 1). Seventy one patients (65%) underwent subsequent revascularisation procedures (percutaneous coronary intervention in 39 patients and coronary bypass surgery in 32 patients) (table 1). Among the 104 patients who survived to one year of follow up, the use of aspirin ($p = 0.33$), β blocking agents ($p = 0.72$), diuretics ($p = 0.25$), or angiotensin converting enzyme inhibitor/angiotensin II antagonist ($p = 0.92$) did not differ between groups from hospital discharge to one year of follow up.

## Dobutamine–atropine stress echocardiography

DASE was terminated due to reaching the target heart rate in 71 patients (65%), maximum dose in 11 (10%), severe angina in 18 (17%), non-sustained ventricular tachycardia in 5 (5%), atrial fibrillation in 3 (3%) and hypotension in 1 (1%). The increase in heart rate from rest to peak dobutamine infusion was not significantly different between groups ($p = 0.19$) and did not correlate with the change in MPI from rest to peak DASE in group 1 ($r = 0.17$, $p = 0.94$), group 2 ($r = 0.08$, $p = 0.55$) or group 3 ($r = -0.11$, $p = 0.54$).

Table 3 shows changes during DASE in the individual time intervals combined in the MPI. MPI improved at low dose or at peak stress because of a pronounced shortening of isovolumic times relative to the shortening of ejection time, whereas MPI deteriorated at low dose or at peak stress because of unchanged or even prolonged isovolumic relaxation time relative to a significant shortening of ejection time.

## MPI response during DASE and relationship to NT-pro-BNP

NT-pro-BNP concentration was significantly higher in group 3 than in groups 1 and 2, whereas groups 1 and 2 did not differ (table 1). On univariate regression analysis, raised NT-pro-BNP was associated with an increase in MPI from rest to low dose ($\beta = 0.48$, $p < 0.0001$) and to peak dobutamine infusion ($\beta = 0.31$, $p = 0.001$). On multivariate regression analysis, the association between NT-pro-BNP concentration and MPI response at low dose ($\beta = 0.30$, $p = 0.004$) and at peak dose ($\beta = 0.31$, $p = 0.001$) remained after adjustment for potential confounders such as age, LV systolic function (ejection fraction and wall motion score index), advanced LV diastolic dysfunction (E wave deceleration time ⩽ 140 ms), moderate to severe mitral regurgitation and right ventricular dysfunction (defined as right ventricular end diastolic diameter ⩾ 20 mm/m$^2$ and akinesis ⩾ 1 right ventricular segment or interventricular septal paradoxical motion).

## MPI response during DASE and relationship to outcome

During follow up of 27 (7) months, eight patients died of cardiac causes, nine were readmitted to hospital for myocardial reinfarction and six were readmitted for congestive heart failure. No events occurred in group 1 during follow up. In contrast, in group 2, one patient died and four were readmitted for reinfarction or heart failure, and in group 3, seven died and 11 were readmitted. Event rate did not differ between groups 1 and 2 ($p = 0.15$), whereas it increased significantly in group 3 (fig 2).

Among 31 patients with regional wall motion analysis suggesting a non-ischaemic response to DASE, 13 patients had an increase in MPI, indicative of deterioration of LV function during DASE. The event rate among these patients was significantly increased (7 of 13 *v* 0 of 18, log rank 13.9,

**Table 2** Echocardiographic characteristics

| | All patients (n = 109) | Group 1 (n = 21) | Group 2 (n = 53) | Group 3 (n = 35) |
|---|---|---|---|---|
| LV ejection fraction (%) | 45 (10) | 50 (10) | 47 (8) | 39 (10)*† |
| LV end systolic volume index (ml/m$^2$) | 42 (19) | 37 (18) | 42 (21) | 45 (16) |
| LV end diastolic volume index (ml/m$^2$) | 75 (22) | 72 (18) | 73 (26) | 72 (16) |
| WMSI at rest | 1.40 (0.32) | 1.30 (0.35) | 1.33 (0.30) | 1.57 (0.28)*† |
| WMSI at low-dose DASE | 1.22 (0.27) | 1.12 (0.24) | 1.13 (0.20) | 1.43 (0.27)*† |
| WMSI at peak DASE | 1.41 (0.29) | 1.16 (0.28) | 1.37 (0.23) | 1.60 (0.26)‡ |
| Infarct-zone viability | 80 (73%) | 19 (91%) | 48 (91%) | 13 (37%)*† |
| Diastolic function | | | | |
| Normal | 53 (49%) | 13 (62%) | 39 (74%) | 1 (3%)*† |
| Impaired relaxation (grade 1) | 17 (16%) | 5 (24%) | 8 (15%) | 4 (11%) |
| Pseudonormalisation (grade 2) | 34 (32%) | 3 (14%) | 5 (9%) | 26 (74%)*† |
| Restrictive (grade 3) | 5 (5%) | 0 (0%) | 1 (2%) | 4 (11%) |
| Isovolumic relaxation time (ms) | 78 (15) | 85 (16) | 77 (13) | 76 (16) |
| Isovolumic contraction time (ms) | 57 (25) | 48 (28) | 52 (22) | 70 (23)*† |
| Ejection time (ms) | 273 (32) | 278 (28) | 280 (28) | 258 (36)† |
| MPI at rest | 0.51 (0.14) | 0.48 (0.13) | 0.47 (0.13) | 0.58 (0.13)† |
| MPI at low-dose DASE | 0.47 (0.18) | 0.40 (0.13) | 0.39 (0.14) | 0.63 (0.17)*† |
| MPI at peak DASE | 0.55 (0.23) | 0.32 (0.14) | 0.53 (0.16) | 0.71 (0.23)‡ |
| MPI change from rest to low-dose DASE | 0.03 (0.08) | 0.08 (0.05) | 0.08 (0.05) | −0.06 (0.06)*† |
| MPI change from rest to peak DASE | −0.04 (0.16) | 0.17 (0.06) | −0.06 (0.09) | −0.14 (0.18)‡ |

Data presented as mean (SD) or number (%) of patients.
*p<0.05 versus group 1; †p<0.05 versus group 2; ‡p<0.001 for all comparisons between groups.
DASE, dobutamine–atropine stress echocardiography; LV, left ventricular; MPI, myocardial performance index; WMSI, wall motion score index.

$p < 0.0001$). Among these 13 patients, seven underwent revascularisation (percutaneous coronary intervention in three patients and coronary artery bypass grafting in three; one patient underwent both procedures).

Table 4 shows univariate predictors of cardiac events. In a multivariate model including age, LV ejection fraction at rest, diastolic dysfunction, anterior infarct location, new or worsened wall motion abnormalities with stress, an increase in MPI from rest to low dose, an increase in MPI from low dose to peak stress and NT-pro-BNP, only an increase in MPI at low-dose DASE (hazard ratio 6.3, 95% confidence interval 1.4 to 28.7; $p = 0.018$) proved to be an independent predictor of cardiac events. Traditional wall motion analysis during DASE provided no additional prognostic information.

### Reproducibility

The intraobserver variability for MPI was 2 (3)% at rest, 2 (4)% at low dose and 2 (6)% at peak dobutamine dose. The interobserver variability for MPI was 2 (4)% at rest, 1 (6)% at low dose and 4 (7)% at peak dobutamine dose. Variability of MPI from rest to peak dobutamine infusion did not increase significantly when assessed by the same observer ($p = 0.14$) or by different observers ($p = 0.20$).

## DISCUSSION

This study shows in hospital survivors after AMI that an increase (deterioration) in MPI during low-dose dobutamine echocardiography is associated with increased neurohormonal activation and increased risk of cardiac events. With MPI available, conventional wall motion analysis during peak-dose dobutamine stimulation provided no additional prognostic information.

### Added value of MPI response during DASE

Myocardial ischaemia is known to impair both diastolic and systolic LV function; diastolic abnormalities precede systolic abnormalities.[4] MPI integrates systolic and diastolic time intervals. With the onset of ischaemia, the sum of isovolumic times is prolonged and ejection time shortens and, consequently, MPI increases. An increase in MPI during DASE has been proposed as a sensitive marker of myocardial ischaemia.[7]

In the healthy heart, dobutamine reduces the isovolumic times due to its positive inotropic and lusitropic effects.[21] Thus, LV performance is maximised with a greater part of the cardiac cycle occupied with either ejection or filling, and isovolumic times, when the ventricle is neither ejecting nor filling, are reduced.[22] In patients with inducible ischaemia, however, this shortening of isovolumic times is absent or even reversed, reducing the time for diastolic filling.[23 24] Accordingly, we observed a reduced shortening of isovolumic times relative to ejection time among patients with deterioration of MPI during DASE. Thus, these patients seem to have a paradoxical response to dobutamine with a reduced filling time—that is, the diastolic period is abnormally shortened, reducing time available for coronary artery filling. This may perpetuate subsequent myocardial perfusion instabilities. In

**Table 3** Changes in isovolumic times, ejection time and MPI during DASE in the three study groups

| | Group 1 | | | Group 2 | | | Group 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Rest | Low dose | Peak DASE | Rest | Low dose | Peak DASE | Rest | Low dose | Peak DASE |
| IRTc | 90 (18) | 77 (17)* | 56 (20)* | 79 (14) | 71 (17)* | 82 (23) | 82 (16) | 86 (17) | 91 (29) |
| ICTc | 50 (30) | 35 (24)* | 25 (26)* | 54 (24) | 31 (23)* | 43 (31)* | 76 (25) | 75 (32) | 72 (37) |
| ETc | 292 (20) | 287 (22) | 254 (19)* | 287 (19) | 283 (17) | 238 (24)* | 278 (24) | 269 (25)* | 233 (27)* |
| MPI | 0.48 (0.13) | 0.40 (0.13)* | 0.32 (0.14)* | 0.47 (0.13) | 0.39 (0.14)* | 0.53 (0.16)* | 0.58 (0.13) | 0.63 (0.17)* | 0.71 (0.23)* |

Data presented as mean (SD).
*p<0.05 versus resting values within groups.
DASE, dobutamine–atropine stress echocardiography; ETc, heart rate corrected ejection time; ICTc, heart rate corrected isovolumic contraction time; IRTc, heart rate corrected isovolumic relaxation time; MPI, myocardial performance index.

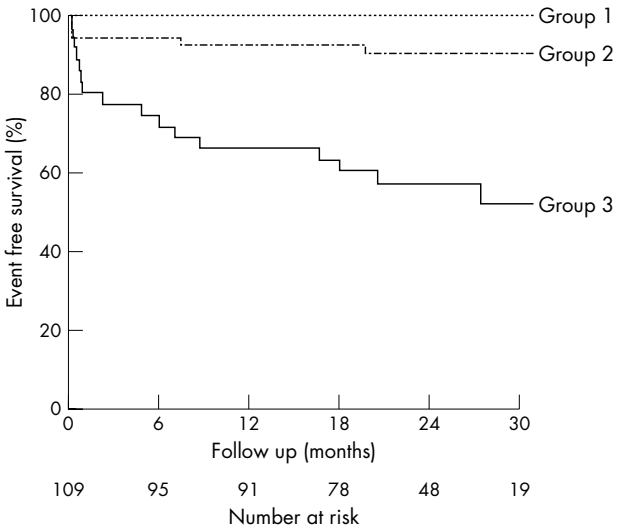


**Figure 2** Kaplan–Meier event-free survival estimates for cardiac events in the three study groups. The cumulative event-free survival was significantly lower in group 3 than in groups 1 ($p < 0.0001$) and 2 ($p = 0.0004$), whereas groups 1 and 2 did not differ significantly ($p = 0.15$).

the presence of compromised coronary flow reserve, stimulation of the myocardium by even a low dose of dobutamine may precipitate myocardial ischaemia by increasing the oxygen demand beyond the already compromised threshold,[25] possibly explaining the increase in MPI even at low-dose dobutamine stimulation in these patients. Repetitive ischaemic episodes in jeopardised areas may be expected to lead to a progressive loss of potentially viable myocytes, mechanical dysfunction and cardiovascular events.

## BNP and inducible ischaemia

Few studies have related inducible ischaemia to BNP concentration. Bibbins-Domingo *et al*[13] reported that raised BNP concentration at rest is independently associated with exercise-induced ischaemia among patients with stable coronary artery disease, particularly among those with a previous myocardial infarction. In another study of 35 patients with known angina,[14] BNP concentration increased after exercise. The degree of BNP rise correlated with the size of the ischaemic territory, suggesting that inducible ischaemia may lead to raised BNP concentration. In our study, an increase in MPI during DASE was independently associated with raised BNP concentration. Accordingly, both prognostic indices appear to point in the same direction. Although the pathophysiology underlying this observation remains to be clarified, one can speculate that jeopardised infarct areas contribute to an increased load and increased wall stress in the remaining non-infarcted myocardium, stimulating release of cardiac peptides. The observed high NT-pro-BNP concentration and advanced degree of LV diastolic dysfunction in group 3 patients suggest raised filling pressures, which may further compromise coronary artery filling. These factors would be expected to increase the risk of cardiovascular events. This is further supported by recent invasive studies showing a positive correlation between MPI and LV filling pressure.[26 27]

## Clinical implications

By introducing evaluation of MPI during DASE, we were able even with low-dose dobutamine infusion to identify a group of patients with deterioration of overall LV function, where conventional wall motion analysis did not show deterioration in LV systolic function. These patients were at high risk of adverse outcomes. Thus, MPI analysis is likely to be an important step in the effort to objectively and sensitively detect overall LV dysfunction during dobutamine stress echocardiography. This method may therefore assist in the risk stratification of patients early after AMI.

Identifying LV dysfunction even during low-dose dobutamine echocardiography confirms the previous studies of Tsutsui *et al*,[28 29] who showed the usefulness of determining the myocardial velocity gradient by tissue Doppler imaging to detect myocardial ischaemia during only submaximal dobutamine challenge. The consistency between our results and those of Tsutsui *et al*,[28 29] although we used different quantitative techniques to explore myocardial ischaemia, further enhances the strength of our findings.

## Limitations

At the time of DASE, 92% of all patients were treated with β blocking agents. Although treatment was discontinued 24 hours before stress testing, this could have interfered with the detection of ischaemia. Treatment with β blocking agents was evenly distributed between groups, however, and, given the well-documented beneficial effects of adrenergic β blockade after AMI, withholding β blockers would be unethical.

MPI has been reported to increase at increasing heart rates,[30] and one can speculate that the changes in MPI during DASE vary between groups due to differences in heart rate response. But this seems unlikely, as the increase in heart rate was comparable between groups and did not correlate with the changes in MPI in any of the groups. Moreover, MPI has been shown to correlate with LV systolic function during dobutamine infusion independently of the increase in heart rate.[5]

**Table 4** Univariate Cox regression analysis for prediction of cardiac events

| | Wald $\chi^2$ | Hazard ratio (95% CI) | p Value |
|---|---|---|---|
| Age | 11.31 | 1.07 (1.03 to 1.10) | 0.001 |
| LV ejection fraction | 11.45 | 0.94 (0.90 to 0.97) | 0.001 |
| Diastolic dysfunction* | 14.35 | 2.49 (1.55 to 3.99) | <0.0001 |
| Anterior infarct location | 0.34 | 0.77 (0.31 to 1.90) | 0.56 |
| WMSI at rest | 7.08 | 4.11 (1.45 to 11.64) | 0.01 |
| WMSI at low dose | 12.25 | 9.02 (2.63 to 30.91) | <0.0001 |
| WMSI at peak stress | 7.39 | 5.09 (1.57 to 16.47) | 0.01 |
| Inducible ischaemia | 0.23 | 0.80 (0.32 to 1.98) | 0.63 |
| MPI increase from rest to low dose | 17.07 | 8.35 (3.05 to 22.83) | <0.0001 |
| MPI increase from low dose to peak stress | 3.98 | 7.74 (1.04 to 57.70) | 0.046 |
| Log NT-pro-BNP | 17.98 | 3.90 (2.08 to 7.33) | <0.0001 |

*Calculated for an increase of one grade in diastolic dysfunction.
NT-pro-BNP, N-terminal pro-brain natriuretic peptide; LV, left ventricular; MPI, myocardial performance index; WMSI, wall motion score index.

Revascularisation after AMI could not be standardised and may have affected the prognostic significance of DASE. The excess of revascularisation procedures in group 2 compared with group 1 may explain, at least in part, the low event rate in group 2 patients. Therefore, adjustment for revascularisation procedures in Cox regression analysis would be desirable. Revascularisation was performed relatively late, however, reflecting that the study was done before widespread use of primary angioplasty and even with some delay of treatment for patients with non-ST segment elevation AMI. Thus, patients eligible for revascularisation were those who survived the early postinfarction period irrespective of revascularisation. Inclusion of revascularisation in the prognostic models would therefore introduce a major bias, as the model would not be able to separate the effect of surviving the early post-AMI period from the effect of revascularisation.

As patients with an increase in MPI during low-dose DASE presented more commonly with multivessel disease, outcome may be significantly improved by selective use of revascularisation in these high-risk patients. Given the regional location of coronary artery disease, this technique should be regarded as adjunctive and not specific to a certain myocardial region and targeted revascularisation. Future studies are needed to establish the potential beneficial effect of revascularisation procedures or adjunctive treatments aimed at improving tissue perfusion in these patients.

## Conclusions

After a first AMI, evaluation of the MPI response during DASE enhances the prognostic yield of traditional wall motion analysis during DASE. Moreover, an increase (deterioration) in MPI at the low-dose stage is independently associated with raised NT-pro-BNP concentration and increased risk of cardiac events. With MPI available, traditional wall motion analysis during DASE provides no additional prognostic information.


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